Surgeons' Ability to Predict the Extent of Surgery Prior to Cytoreductive Surgery With Hyperthermic Intraperitoneal Chemotherapy

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Postoperative neurocognitive disorders

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Abstract

A decline in cognitive function is a frequent complication after major surgery. Postoperative cognitive impairments have generally been divided into short (postoperative delirium) and long-term disturbances (postoperative cognitive dysfunction [POCD]). Long-term impairments are often subtle and overlooked. They need to be objectively assessed with neuropsychological tests in order to be diagnosed. Although POCD has been the subject of considerable research over the past decades, it remains uncertain why some patients do not return to preoperative levels of cognitive function. Surgery and anesthesia have both been implicated in playing a role in developing POCD, and certain patient-related factors, such as advanced age and low preoperative baseline cognitive function have consistently been found to predict postoperative cognitive decline. This article will provide an overview of POCD, and its etiology, and provide advice on possible strategies on preventing it.

Keywords: Aged; Delirium; Frail elderly; Inflammation; Neurocognitive disorders; Perioperative care; Postoperative cognitive complications.

Introduction

It has been over five decades since P.D. Bedford observed that surgery in elderly patients was followed by a significant cognitive decline that lasted for an extensive period of time [1]. Through interviews (with patients and relatives) and subjective assessment, he found that 7% of his (elderly) patients who underwent surgery and received general anesthesia had developed signs of cognitive impairment. He published these findings in The Lancet, concluding that 'the allegation "He's never been the same since his operation " is sometimes true, and that an irreversible gross dementia is occasionally the aftermath of surgical operations under general anesthesia [1].'

By the late 1980s psychometric tests were being used to objectively assess cognitive decline after surgery, particularly in patients undergoing cardiac surgery [2]. These studies too, consistently documented long-term cognitive disorder in elderly patients, although with varying incidences and severity. As a result, the concept postoperative cognitive dysfunction (POCD) developed as a diagnosis based on these objective measurements. Although surgery and anesthesia have improved dramatically since then, our exact understanding of when, how and why some patients do not return to baseline cognitive function remains elusive. As cognitive dysfunction, in the form of delirium has been shown to be important for perioperative outcome and mortality [3–5], it is also important to consider the effects of long-term cognitive impairment and its possible risk factors. In this review, we present a brief overview of POCD and its etiology, and provide advice on possible strategies on preventing it.

Postoperative cognitive impairment; delirium and POCD

Cognitive impairment after surgery is common, particularly in elderly patients. These impairments have generally been divided into short (delirium) and long-term disturbances (postoperative cognitive dysfunction [POCD]) [6]. The former is familiar among many clinicians

and well-defined according to the Diagnostic and Statistical Manual of Medical Disorders (DSM)-5 [7]. It states that delirium consists of impairments in attention, awareness and cognition. Cognition is considered to be a dynamic state, involving multiple domains such as memory, orientation, language, visuospatial ability or perception [8]. It fluctuates throughout the day, and is affected by both endogenous and exogenous factors [9]. The incidence of postoperative delirium is reported to be between 20–45% of the older adult surgery patients [10,11].

The term POCD on the other hand, has been used to refer to any signs of new cognitive impairment that exceeds the expected length of time needed to recover from the acute effects of surgery and anesthesia [6,12,13]. Unlike delirium, which is a relatively simple and recognizable syndrome, POCD is clinically far less apparent as it often only manifests as mild cognitive decline in one or more cognitive domains [6,14,15]. Furthermore, the DSM-5 does not list POCD as a diagnosis. In 2018, this prompted an expert panel of scientists and clinicians, The International Perioperative Cognition Nomenclature Working Group, to address, clarify and give structure to POCD and other perioperative cognitive impairments, whilst proposing new nomenclature to be used in relation to these terms [16].

This working group stated that all cognitive changes associated with surgery and anesthesia should be summarized under the term ‘perioperative neurocognitive disorders,’ thus aligning these impairments with the clinical diagnostic criteria for ‘neurocognitive disorders (NCD)’ already applied in the DSM-5 [7,16]. The working group recommends assessing POCD at least 30 days after surgery, at which point most patients are expected to have recovered, physically, physiologically and emotionally from surgery and hospitalization [16]. If assessed too early, the effects of POCD may be overshadowed by acute postoperative delirium or by other cognitive complications that may arise from immobility, sleep deprivation and ongoing pharmacological

interventions [2]. When cognitive impairment manifests itself beyond 12 months after surgery, mild or major [e.g. dementia] Neurocognitive Disorders should be considered over POCD [16].

The term 'delayed neurocognitive recovery' may be used to describe a cognitive disorder that is detected within 30 days after surgery when delirium has been excluded. Table 1 summarizes the recommendations offered by the working group [9,16].

Assessing POCD

Unlike delirium, the diagnosis POCD has primarily been confined to research. Its diagnosis relies on objectively measurable cognitive decline assessed with neuropsychological tests [12,13,17]. Subjective reports of cognitive changes by patients or proxies are also relevant, however, most studies comparing cognitive complaints and neuropsychological test results were unable to find a significant correlation [13,18]. Certain cognitive functions may be less relevant to a patient's daily life, and as such, any dysfunction may be overlooked by the patient. There is no agreed upon definition for POCD, but it generally refers to impairment of memory, learning, concentration, attention or psychomotor performance [12,16]. Neuropsychological tests are often specific to one of these cognitive domains.

Neuropsychological tests that were used in a key international multicenter study on POCD (the International Study of Post-Operative Cognitive Dysfunction, ISPOCD 1) are described in Table 2. There are a wide variety of neuropsychological tests, which all have different levels of sensitivity, and reliability. The ISPOCD mostly used written tests. Our research group, however, favors computerized tests, such as the Cogstate Computerized Cognitive Test Battery ®, because of its ease of use, versatility and the availabilit of age-matched control group test data.

Certain tests are more vulnerable to the effects of practice, and have a poor test-retest reliability [9,13,17]. Others, notoriously suffer from floor and ceiling-effects resulting from tests being either

too difficult or too easy to detect subtle changes [13]. The method with which these test results are interpreted also varies throughout literature [2]. Test batteries, consisting of multiple tests are able to assess various cognitive domains and are recommended as they are able to describe the brain functions in more detail and sensitivity [2,13]. To measure cognitive decline, investigators should determine the change between baseline preoperative cognitive function and postoperative cognitive function. In order to correct for age-related test-retest variability, determining the change in cognitive function with the use of the reliable change index (RCI) is recommended, as it calculates this change with reference to the expected change found within an age-matched control group [13].

Incidence of POCD

The incidence of POCD ranges from 20 to 50% of older patients 3 months after cardiac surgery and in 5 to 55% of those undergoing major noncardiac surgeries [12,19–23]. This large variation is the result of the methodological differences between studies, making comparison of data often difficult. In addition to the various types of test that may be administered for measuring cognitive change, the degree of change and cut-offs necessary for determining POCD have also varied throughout literature. Generally, POCD is divided into mild or major neurocognitive decline, if testing exhibits a decline of > 1 or > 2 standard deviations of cognitive function compared to preoperative cognitive performance, respectively. As described above, the timing of tests is also a known source of variability; the later the cognitive assessment is conducted and the more stringent statistical criteria for identifying POCD, the lower the reported incidence [13].

This point is illustrated by the large multicenter ISPOCD study conducted in 1998, which observed 1000 patients (> 60 years) undergoing various noncardiac surgeries [12]. A comprehensive neuropsychological test battery was administered with a strict criterion for POCD. This study found that 25.8% (95% CI, 23.1–28.5) of patients showed signs of cognitive dysfunction

1 week after surgery. Cognitive dysfunction at 3 months after surgery was 9.9% (95% CI, 8.1–12.0). A later study by Monk et al., found similar incidences of POCD in 365 patients undergoing noncardiac surgery; 41.4% (95% CI, 36.2–46.7) at discharge and 12.7% (95% CI, 8.9–16.4) at 3 months [23]. A recent systematic review of 24 studies found that the incidence of POCD at 3 months was 11.7% (95% CI 10.9–12.5), although they concluded that major differences in methodology and definitions accounted for variations in the results [24].

Pathogenesis of POCD

Despite a growing volume of research concerning POCD, the exact etiology for cognitive decline after surgery and anesthesia is still not well understood. Surgery-, anesthesia- and patient-related factors have all been implicated in playing a role in developing POCD, and support for various hypotheses have changed markedly over the years. Historically, a poor cognitive outcome after surgery was often regarded to be the consequence of cerebral hypoperfusion and hypoxemia [2,14]. Indeed, inadequate cerebral oxygenation will result in brain damage and cognitive decline. Although intuitively compelling, no strong evidence has been found in favor of POCD being the direct consequence of impaired cerebral hemodynamics and oxygenation [2,22,25]. This was also confirmed by the ISPOCD, which monitored perioperative blood pressure and oxygenation and showed that POCD occurred in the absence of perioperative hypoxemia or hypotension [12].

Factors such as the type and duration of surgery and anesthesia, have also often been presumed to be associated with the incidence of POCD. However, this has not yet been conclusive. A comprehensive study by Evered et al. [19] compared the incidence of POCD after coronary angiography under sedation, total hip replacement and coronary artery bypass graft under general anesthesia. Interestingly, the incidence of POCD was similar and thus independent of the nature of surgery or type of anesthesia administered. Furthermore, evidence on whether volatile or

intravenous anesthetics may be related to POCD has also been controversial and conflicting [26]. Moreover, other studies have not found any correlation between regional or general anesthesia and the incidence of POCD, which further supports the argument that the type of anesthesia appears to be unrelated to the occurrence of POCD [27,28]. It is therefore unlikely that POCD is solely caused by anesthesia or surgery.

A recurring theme and the current rationale for the pathogenesis of cognitive dysfunction encompasses the role of an inflammatory response to surgery and anesthesia [2,14,25]. It is commonly known that inflammatory processes, such as those associated with pneumonia or a urinary tract infection, are regularly accompanied by cognitive decline, particularly in the elderly [29,30]. Extending this model to postoperative cognitive dysfunction, it is thought that the release of proinflammatory mediators, triggered by peripheral surgical stress or trauma, may result in an exaggerated systemic inflammatory response leading to neuroinflammation in vulnerable individuals [14,25,31]. The release of inflammatory cytokines is known to lead to endothelial dysfunction, and also the disruption of tight junctions, which results in an increased blood-brain-barrier (BBB) permeability [25,32]. Consequently, systemic inflammatory cytokines will penetrate the BBB, triggering neuroinflammation and the activation of the neuronal immune system, including microglia and astrocytes [25,31,33]. Inflammatory mediators are also produced within the brain, as a result of peripheral-to-central signaling via humoral and neuronal pathways [34]. The consequences of this immune response are healing, but if excessive, it may also result in further (cerebral) tissue damage in the form of increased synaptic dysfunction, inhibition of neurogenesis, and neuronal death [25].

In mouse models, surgery caused hippocampal-dependent memory impairment that was associated with increased expression of plasma cytokines, as well as reactive microgliosis and interleukin (IL)-1β transcription and expression in the hippocampus [35,36]. By inhibiting IL-1β,

these neuroinflammatory changes were mitigated. Another study showed that tumor necrosis factor (TNF)-α inhibition was also able to limit the release of IL-1 and prevent neuroinflammation and cognitive decline in mice [37]. Thus, peripheral surgical injury can result in inflammation and neuroinflammation. However, interpreting and judging the significance of an inflammatory markers is challenging, as inflammation is a normal physiological response to injury [25].

Generally, inflammation is only harmful when proinflammatory responses outweigh the anti-inflammatory response. Certain patient-related factors are known to exacerbate proinflammatory responses or result in some patients being more vulnerable to the effects of inflammation. Advanced age has been consistently associated with POCD throughout the literature [2,9]. Structural cerebral changes, such as a reduction in grey matter volume and myelinated axon length are normal changes that occur with aging [25,38]. The normal decline of cognitive function in the elderly might possibly be further exacerbated by the loss of neuronal dendrite spines, as well as alterations in synaptic transmission and receptors [39]. Furthermore, blood-brain-barrier dysfunction has also been found in older patients even in the absence of surgery [40]. This decline in 'cognitive reserve' may thus explain how elderly patients are more susceptible to effects of inflammation and therefore neuronal injury. A low preoperative cognitive function, and lower education level have also been frequently associated with POCD, also suggesting the vulnerability of a reduced 'cognitive reserve' [2,12,23,41].

Predisposing patient factors may also exaggerate an inflammatory response, as a result of 'immune priming' [25]. For instance, normal aging without any comorbidities has been associated with a low-grade inflammatory activity and increased levels of plasma tumor necrosis factor-α and IL-6 compared to younger patients [42]. Elderly patients are also more susceptible for sepsis [43]. It is unsurprising that patients of advanced age may be more likely to develop an exaggerated inflammatory response as a consequence of surgery. The immune system activation caused by

atherosclerosis, or neurogenerative disorders such as Alzheimer's and Parkinson's, may also prime individuals to develop an excessive inflammatory response [44,45]. The presence of Alzheimer's dementia biomarkers in cerebrospinal fluid has been shown to be associated with POCD at 3 months, which has also led to the notion that they may involve similar mechanisms [46].

Considering the role of inflammation, several studies have attempted to prevent postoperative cognitive dysfunction with anti-inflammatory drugs [14,47]. One study on the effects of high-dose intraoperative dexamethasone administration in cardiac surgery, showed that it did not reduce the risk of POCD [48]. Furthermore, other studies have found that lidocaine, magnesium and complement cascade inhibitors also failed to prevent POCD [49–51]. These negative findings and the understanding that not all elderly patients undergoing major surgery develop POCD or not all patients with atherosclerosis develop POCD after cardiac surgery, reflects the pathophysiological complexity of POCD.

Prevention of POCD

Although a firm understanding for the causes of POCD is absent, improving cognitive outcome after surgery remains an important objective for anesthesiologists and surgeons alike. To date, no pharmacological intervention has convincingly been shown to mitigate the incidence or magnitude of POCD [14]. Dexmedetomidine, an anesthetic agent with neural anti-inflammatory effects, has been found to be potentially effective at reducing the incidence of postoperative delirium, however any evidence that it may be effective at reducing POCD is incomplete [52,53]. Deep sedation has also been identified as a risk factor for delirium, and several studies have found that measuring the depth of anesthesia (with electroencephalogram monitors) was effective at reducing postoperative delirium, however, there is conflicting evidence that POCD can also prevented with the same measures [54–58]. If possible, deliriogenic [pre]medications such as benzodiazepines should also

be avoided [59,60]. Pain and increased post-operative opioid consumption are known to increase the risk of delirium and have also been associated with POCD [60]. Although sufficient pain-management is mandatory, opioid-sparing analgesia may be an effective measure at alleviating some of this risk. Early postoperative mobilization, and a fast-track postoperative approach may help in this respect [61].

Generally, for [non-pharmacological] preventive measures to be significantly effective, multiple (interdisciplinary) interventions, covering various domains, should be considered [2,9,14]. Patients with a possible high risk for POCD should be identified preoperatively and cognitively assessed. When possible, predisposing factors should be modified and adjusted so that patients are sufficiently prepared for surgery. Preparing patients, and their relatives, adequately by informing them about possible postoperative cognitive changes is also beneficial [62]. Extended periods of preoperative fasting and dehydration should be avoided, as should unnecessary postponement of surgery [63]. Peri-and postoperative patient (re)orientation is essential. Encouraging patients to wear their glasses and hearing aids, and early removal of catheters and lines are known to be effective at reducing postoperative delirium, and will help orientate patients and mobilize them earlier, which may likely be effective at preventing POCD [60].

Numerous novel approaches that have been shown to improve cognitive function in older adults have also been proposed as possible interventions that may prevent, or protect patients against postoperative cognitive dysfunction. These proposed interventions involve diet interventions, physical exercise programs, and brain stimulation and cognitive training [14,64]. Although these strategies are known to improve overall cognition, few of them have been investigated as potential and feasible interventions for POCD [2]. One study by Kawano et al. [65] found that preoperative environmental enrichment (PEE), consisting of both cognitive and physical activity, was able to attenuate neuroinflammation and improve cognitive function in old rats after abdominal surgery. In

humans, there is some evidence that preoperative physical status may improve postoperative morbidity, however, cognitive advantages, if any, are not yet known [66,67]. Nonetheless, for treatments for cognitive decline there appears to be some potential in improving lifestyle-based factors, although further investigation is necessary.

Conclusion

In summary, many studies have drawn attention to neurocognitive dysfunction after surgery by using neuropsychological assessments prior to and after surgery. Results on the incidence and severity of postoperative cognitive decline is varying, mostly due to varying definitions for diagnosing postoperative cognitive dysfunction. The incidence of POCD in older patients at 3 months ranges from 20 to 50% after cardiac surgery and 5 to 55% major noncardiac surgeries [12,19–23].

Although the etiology of postoperative cognitive dysfunction is still not fully understood, inflammatory-processes are currently considered to be central to its genesis. At the present time, no clear anesthetic and surgical components have been found to influence POCD. Nevertheless, several patient-related factors, such as advanced age, have been associated with an increased risk for cognitive decline. As the age of the general population undergoing surgery is growing older, investigations on preventive measures and interventions are warranted and they should be aptly applied.

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Table 1. A Summary of the Recommendations for the New Nomenclature of Perioperative Disorders, from The International Perioperative Cognition Nomenclature Working Group [16].

Terms	Time period
Neurocognitive disorder [mild or major [e.g. dementia]]	Pre-existing/preoperative cognitive impairment *or c*ognitive impairment developing after 12 months of surgery.
Emergence delirium	Delirium diagnosed within minutes or hours after surgery.
Postoperative delirium	Delirium diagnosed within days after surgery, up to 1 week or until discharge.
Delayed neurocognitive recovery	Cognitive decline up to 30 days after surgery.
Postoperative [neuro]cognitive dysfunction	Cognitive impairment detected between 30 days up to 12 months after surgery.

Table 2. Neuropsychological Tests Used in the in the International Study of Post-Operative Cognitive Dysfunction 1 (ISPOCD 1) Study

Tests	
Mini-mental state examination [MMSE] [68]	A commonly used assessment, initially developed to evaluate dementia. It assesses multiple cognitive domains including attention, memory and orientation.
Visual verbal learning test [69]	Based on Rey's auditive recall test. It assesses verbal memory, by asking patients to recall a list of words that they were presented with earlier.
Concept Shifting test [trail-making test] [70]	Also known as the trail-making tests A and B. It is used to assess executive function and attention, by asking subjects to connect a series of consecutive numbers, letters or both as quickly as possible.
Stroop color word interference test [71]	This test evaluates the ability to inhibit cognitive interreference from multiple congruent and incongruent stimuli.
Letter-digit coding test [symbol-digit substitution task] [72]	Used to assess executive function. Patients are presented with a series of digits and letters that are paired and another list of only digits. They are then asked to write the corresponding letter as fast as possible.
Four boxes test [73]	This test is computer-based. It is used to measure reaction time, by asking patients to select a black circle in one of four boxes on a screen as quickly as possible.